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Search:

drug delivery system
radioimmunoconjugate?

① An Immunconjugate comprising therapeutic agent and an antibody binds to a Lewis Y cell membrane Ag & when upon binding to the Ag, the antibody is internalized

② BR96 antibody

③ ~~Agg~~ Ab binds to a fucosylated variant of a Lewis Y Ag

delivery systems
dosage forms
pharmaceutical
dosage forms

antibody conjugates

IgG
immunotoxin
monoclonal antibody
conjugates
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E5 1 BRA-3 LECTIN (MEGABALANUS ROSA CLONE BRA3-12Z)/CN

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br 96)

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CONJUGAT?

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L11 13 DUP REM L10 (19 DUPLICATES REMOVED)

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L11 ANSWER 1 OF 13 MEDLINE DUPLICATE 1
2000291215 Document Number: 20291215. Phase I trial of the anti-

Lewis Y drug **immunoconjugate BR96**

-doxorubicin in patients with **lewis Y**-expressing

epithelial tumors. Saleh M N; Sugarman S; Murray J; Ostroff J B; Healey

D;

Jones D; Daniel C R; LeBherz D; Brewer H; Onetto N; LoBuglio A F.

(Department of Medicine, Division of Hematology/Oncology, Comprehensive
Cancer Center, University of Alabama at Birmingham, 35294-3300, USA..

mansoor.saleh@ccc.uab.edu) . JOURNAL OF CLINICAL ONCOLOGY, (2000 Jun) 18
(11) 2282-92. Journal code: JCO. ISSN: 0732-183X. Pub. country: United
States. Language: English.

AB PURPOSE: We conducted a phase I clinical trial of **BR96**

-Doxorubicin (**BR96**-Dox), a chimeric anti-**Lewis**

Y (Le(Y)) **monoclonal antibody**

conjugated to doxorubicin, in patients whose tumors expressed the
Le(Y) antigen. The study aimed to determine the toxicity,

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maximum-tolerated dose, pharmacokinetics, and immunogenicity of **BR96-Dox**. PATIENTS AND METHODS: This was a phase I dose escalation study. **BR96-Dox** was initially administered alone as a 2-hour infusion every 3 weeks. The occurrence of gastrointestinal (GI) toxicity necessitated the administration of **BR96-Dox** as a continuous infusion over 24 hours and use of antiemetics and antigastritis premedication. Patients experiencing severe GI toxicity underwent GI endoscopy. All patients underwent restaging after two cycles. RESULTS: A total of 66 patients predominantly with metastatic colon and breast cancer

25 were enrolled onto the study. The most common side effects were GI toxicity, fever, and elevation of pancreatic lipase. At higher doses, **BR96-Dox** was associated with nausea, vomiting, and endoscopically documented exudative gastritis of the upper GI tract, which was dose-limiting at a maximum dose of 875 mg/m² (doxorubicin equivalent,

generally mg/m²) administered every 3 weeks. Toxicity was reversible and

of short duration. Premedication with the antiemetic Kytril (granisetron hydrochloride; SmithKline Beecham, Philadelphia, PA), the antacid omeprazole, and dexamethasone was most effective in ameliorating GI toxicity. A dose of 700 mg/m² **BR96-Dox** (doxorubicin equivalent, 19 mg/m²) every 3 weeks was determined to be the optimal phase II dose when administered with antiemetic and antigastritis prophylaxis. **BR96-Dox** deposition on tumor tissue was documented immunohistochemically and by confocal microscopy. At the 550-mg/m² dose,

were the half-life (mean +/- SD) of **BR96** and doxorubicin was 300 +/- 95 hours and 43 +/- 4 hours, respectively. **BR96-Dox** elicited a weak immune response in 37% of patients. Objective clinical responses

seen in two patients. CONCLUSION: **BR96-Dox** provides a unique strategy to deliver doxorubicin to Le(Y)-expressing tumor and was well tolerated at doses of 700 mg/m² every 3 weeks. **BR96-Dox** was not associated with the typical side-effect profile of native doxorubicin and can potentially deliver high doses of doxorubicin to antigen-expressing tumors. A phase II study in doxorubicin-sensitive tumors is warranted.

L11 ANSWER 2 OF 13 MEDLINE

DUPLICATE 2

2000182786 Document Number: 20182786. Enhanced delivery improves the efficacy of a tumor-specific doxorubicin **immunoconjugate** in a human brain tumor xenograft model. Remsen L G; Trail P A; Hellstrom I; Hellstrom K E; Neuwelt E A. (Department of Neurology, Oregon Health Sciences University, Portland 97201, USA.) NEUROSURGERY, (2000 Mar) 46 (3) 704-9. Journal code: NZL. ISSN: 0148-396X. Pub. country: United States. Language: English.

AB OBJECTIVE: To evaluate dose intensification with osmotic blood-brain barrier disruption (BBBD) and the potential use of drug targeting with monoclonal antibody (MAb) **BR96** conjugated to doxorubicin (**BR96-DOX**, now called SGN15) for treatment of intracerebral and subcutaneous human LX-1 small cell lung carcinoma xenografts in rats. METHODS: LX-1 tumors with high, low, or heterogeneous levels of the **Lewis(y)** antigen for **BR96** were evaluated. Rats were treated with intracarotid or intravenous **BR96-DOX**, with or without osmotic BBBD. RESULTS: Both **BR96-DOX** and MAb

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BR96 treatment resulted in significant regression of subcutaneous tumors, in contrast to control groups including doxorubicin alone, saline, or nonbinding doxorubicin **immunoconjugate**. BR96-DOX delivered with BBBB to brain tumors with low antigen expression resulted in significantly ($P < 0.001$) increased rat survival time compared with animals that received intravenous or intra-arterial BR96-DOX. CONCLUSION: The combination of an effective drug such as doxorubicin with a MAb to facilitate tumor-selective localization and osmotic BBBB to increase tumor delivery may have practical application in the clinic, because an increased delivery of drug to tumor can be obtained without increasing the dose of systemic drug.

L11 ANSWER 3 OF 13 BIOSIS COPYRIGHT 2001 BIOSIS
2000:355796 Document No.: PREV200000355796. Influence of immunogenicity on the

pharmacokinetics of BMS-191352, a Pseudomonas exotoxin **immunoconjugate**, in rats and dogs. Damle, Bharat (1); Tay, Lee; Comerreski, Charles; Warner, William; Kaul, Sanjeev. (1) Metabolism and Pharmacokinetics, Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ, 08543-4000 USA. Journal of Pharmacy and Pharmacology, (June, 2000) Vol. 52, No. 6, pp. 671-678. print. ISSN: 0022-3573. Language: English. Summary Language: English.

AB BMS-191352 is an immunotoxin construct of modified Pseudomonas exotoxin conjugated to a fragment of the BR96 monoclonal antibody. We have investigated the potential for immunogenicity of BMS-191352 and its influence on the pharmacokinetics in rats and dogs. BMS-191352 was administered intravenously at doses of 0.75, 1.5, and 3 mg m⁻² once every two days for a total of five doses in rats, and 1.2, 2.4, and 4.8 mg m⁻² once every three days for a total of five doses in dogs. Blood samples were collected on days 1 and 9 in rats, and on days 1, 7, and 13 in dogs to monitor pharmacokinetics and anti-BMS-191352 immune response. Plasma concentrations of BMS-191352 and serum anti-BMS-191352 antibody titre were

determined using ELISA assays. Pharmacokinetics were assessed using a non-compartmental method. Anti-BMS-191352 antibodies were not observed in rats within the drug administration interval. In all dogs, except one, markedly higher anti-BMS-191352 antibody titres were observed on day 13 compared with days 1 and 7, and its magnitude was independent of BMS-191352 dose. The single dose kinetics of BMS-191352 in rats and dogs were linear and the drug exposures were generally dose proportional. Mean half-life, total body clearance, and volume of distribution were 1.74 h, 3.35 mL min⁻¹ m⁻², and 0.27 L m⁻² in rats, respectively, and 4.27 h, 6.28 mL min⁻¹ m⁻², 1.19 L m⁻² in dogs, respectively. The multiple-dose (day 9) kinetics in rats were similar to the single-dose kinetics. In dogs, the disposition of BMS-191352 on day 7 was similar to that on day 1; however, there was a precipitous reduction in the systemic drug exposure (by 5- to 110-fold) and marked increase in drug clearance on day 13. These changes in the kinetics of BMS-191352 were attributed to the generation of anti-BMS-191352 antibodies. In the one dog that did not develop anti-BMS-191352 antibodies, the pharmacokinetics were unchanged. The pharmacokinetics of BMS-191352 may be perturbed due to an immune response thus restricting the therapeutic utility of the immunotoxin.

L11 ANSWER 4 OF 13 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 3
2000:495959 Document No.: PREV200000496080. A multi-institutional phase II
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study of BMS-182248-01 (**BR96**-doxorubicin conjugate) administered every 21 days in patients with advanced gastric adenocarcinoma. Ajani, Jaffer A. (1); Kelsen, David P.; Haller, Daniel; Hargraves, Kristin; Healey, Diane. (1) U.T.M.D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX, 77030 USA. Cancer Journal, (March April, 2000) Vol. 6, No.

2, pp. 78-81. print. ISSN: 1528-9117. Language: English. Summary Language: English.

AB PURPOSE: High levels (> 200,000 molecules per carcinoma cell) of the LewisY antigen are expressed on the surface of most (> 75%) gastric carcinomas. The BMS-182248-01 is a chimeric variant of anti-LewisY monoclonal antibody that is conjugated with doxorubicin. In a phase I study, BMS-182248-01 resulted in a partial response in a patient with gastric carcinoma. We, therefore, conducted a multi-institutional phase

II study of BMS-182248-01 in patients with advanced gastric carcinoma. METHODS AND PATIENTS: Only patients with evidence of LewisY antigen by immunohistochemical method on their gastric carcinoma were treated. Patients with unresectable gastric adenocarcinoma were eligible. Patients had to have adequate liver, renal, and marrow functions. Written consent was obtained from all patients. All patients were hospitalized. BMS-182248-01 was administered at the starting dose of 700 mg/m² I.V.

over 24 hours on day 1 every 3 weeks. RESULTS: Fifteen patients were enrolled. There were 10 men and 5 women. The median age at enrollment was 56 years, with ages ranging from 34 to 80 years. No objective responses were observed. Five patients had disease stabilization. The remaining 10 patients progressed on study. Rapidly reversible gastrointestinal toxicity, primarily nausea and emesis, was predominant. There was no neutropenia, thrombocytopenia, or cardiomyopathy. CONCLUSIONS: Although BMS-182248-01 represents a novel approach of **monoclonal antibody conjugated** with an active chemotherapy agent, delivered intracellularly, it was ineffective in patients with gastric carcinoma whose tumors carried LewisY antigen.

L11 ANSWER 5 OF 13 MEDLINE

DUPLICATE 4

2000055697 Document Number: 20055697. Enhanced antitumor activity of paclitaxel in combination with the anticarcinoma **immunoconjugate BR96**-doxorubicin. Trail P A; Willner D; Bianchi A B; Henderson A J; TrailSmith M D; Girit E; Lasch S; Hellstrom I; Hellstrom K E. (Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, New Jersey 08543, USA.) CLINICAL CANCER RESEARCH, (1999 Nov) 5 (11) 3632-8. Journal code: C2H. ISSN: 1078-0432. Pub. country: United States.

Language:

English.

AB The efficacy of chemotherapy has been improved by regimens that combine several cytotoxic drugs with different mechanisms of action and/or different dose-limiting toxicities. Here we demonstrate clearly, and for the first time, that combined therapy using an anticarcinoma **immunoconjugate, BR96**-doxorubicin, and the cytotoxic drug paclitaxel results in a significant increase in antitumor activity over that of either agent alone. Synergistic activity was seen at doses

of

BR96-doxorubicin that were minimally active as single agents. A dramatic increase in regression rates was seen when a regimen that combined **BR96**-doxorubicin and paclitaxel was used to treat both

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paclitaxel-sensitive and paclitaxel-insensitive carcinomas. Importantly, combined therapy resulted in increased antitumor activity against lung, colon, and breast tumors xenografted in athymic mice and large, paclitaxel-insensitive colon tumors xenografted in athymic rats that also express the **Lewis(y)** target antigen in normal tissues.

L11 ANSWER 6 OF 13 MEDLINE

DUPLICATE 5

1999178673 Document Number: 99178673. Randomized phase II study of **BR96**-doxorubicin conjugate in patients with metastatic breast cancer. Tolcher A W; Sugarman S; Gelmon K A; Cohen R; Saleh M; Isaacs C; Young L; Healey D; Onetto N; Slichenmyer W. (British Columbia Cancer Agency, Vancouver, Canada.) JOURNAL OF CLINICAL ONCOLOGY, (1999 Feb) 17 (2) 478-84. Journal code: JCO. ISSN: 0732-183X. Pub. country: United States. Language: English.

AB PURPOSE: BMS-182248-1 (**BR96**-doxorubicin **immunoconjugate**) is a chimeric human/mouse monoclonal antibody linked to approximately eight doxorubicin molecules. The antibody is directed against the **Lewis-Y** antigen, which is expressed on 75% of all breast cancers but is limited in expression on normal tissues. Preclinical xenograft models demonstrated significant antitumor activity, including cures. A randomized phase II design was chosen to estimate the activity

of

the **BR96**-doxorubicin conjugate in metastatic breast cancer in a study population with confirmed sensitivity to single-agent doxorubicin. PATIENTS AND METHODS: Patients with measurable metastatic breast cancer and immunohistochemical evidence of **Lewis-Y** expression on their tumor received either **BR96**-doxorubicin conjugate 700 mg/m² IV over 24 hours or doxorubicin 60 mg/m² every 3 weeks. Patients were stratified on the basis of prior doxorubicin exposure, visceral disease, and institution. Cross-over to the opposite treatment arm was allowed with progressive or persistently stable disease. RESULTS: Twenty-three patients who had received a median of one prior chemotherapy regimen were assessable. There was one partial response (7%) in 14 patients receiving the **BR96**-doxorubicin conjugate and one complete response and three partial responses (44%) in nine assessable patients receiving doxorubicin. No patient experienced a clinically significant hypersensitivity reaction. The toxicities were significantly different between the two treatment groups, with the **BR96**-doxorubicin conjugate group having limited hematologic toxicity, whereas gastrointestinal toxicities, including marked serum amylase and lipase elevations, nausea, and vomiting with gastritis, were prominent. CONCLUSION: The **BR96**-doxorubicin **immunoconjugate** has limited clinical antitumor activity in metastatic breast cancer. The gastrointestinal toxicities likely represent binding of the agent to normal tissues expressing the target antigen and may have compromised the delivery of the **immunoconjugate** to the tumor sites.

L11 ANSWER 7 OF 13 CAPLUS COPYRIGHT 2001 ACS

1998:545386 Document No. 129:188362 Mutant **BR96** antibodies reactive with human carcinomas. Yelton, Dale; Glaser, Scott; Huse, William; Rosok, Mae Joanne (Bristol-Myers Squibb Co., USA). U.S. US 5792456 A 19980811, 71 pp. Cont.-in-part of U. S. Ser. No. 285,936. (English). CODEN: USXXAM. APPLICATION: US 1995-487860 19950607. PRIORITY: US 1994-285936 19940804.

AB The authors disclose the prepn. and improved reactivity of polypeptide muteins of the **BR96** antibody directed to the **Lewis**

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Y determinant. Muteins were constructed using codon mutagenesis of heavy chain CDRs. Application of mutein **immunoconjugates** in cancer diagnosis and treatment is discussed.

L11 ANSWER 8 OF 13 CAPLUS COPYRIGHT 2001 ACS

1997:124811 Document No. 126:195257 Bryodin 2 a ribosome-inactivating protein isolated from the plant Bryonia dioica. Siegall, Clay B.; Gawlak,

Susan L.; Marquardt, Hans (Bristol-Myers Squibb Co., USA). U.S. US 5597569 A 19970128, 41 pp. Cont.-in-part of U.S. Ser. No. 141,891, abandoned. (English). CODEN: USXXAM. APPLICATION: US 1994-324301 19941020. PRIORITY: US 1993-141891 19931025.

AB The present invention discloses a new ribosome-inactivating protein, bryodin 2, isolated from the plant Bryonia dioica. This ribosome-inactivating protein (RIP) is a type-I RIP having a single polypeptide chain and no cellular receptor domain. Like many type-I RIPs,

bryodin 2 has a mol. wt. of about 27,000 daltons and a pI of 9.5.

Bryodin

2 differs from previously identified ribosome-inactivating proteins in its

amino acid compn., amino acid sequence, and toxicity in vitro and in

vivo.

Bryodin 2 is useful, as are other type-I ribosome-inactivating proteins, as an abortifacient, immunomodulator, antitumor, or antiviral agent. Compns. comprising bryodin 2 as an **immunoconjugate** or fusion mol. are particularly useful to kill cells of a target population.

L11 ANSWER 9 OF 13 BIOSIS COPYRIGHT 2001 BIOSIS

1997:139078 Document No.: PREV199799438281. **Immunoconjugates** for therapy of carcinomas. Hellstrom, Karl Erik (1); Firestone, Ray; Trail, Pamela. (1) Bristol-Myers Squibb Pharmaceutical Res. Inst., Seattle, WA USA. Immunotechnology (Amsterdam), (1996) Vol. 2, No. 4, pp. 273. Meeting Info.: 1996 Keystone Meeting on Exploring and Exploiting Antibody and Ig Superfamily Combining Sites Taos, New Mexico, USA February 22-28, 1996 ISSN: 1380-2933. Language: English.

L11 ANSWER 10 OF 13 BIOSIS COPYRIGHT 2001 BIOSIS

1996:253367 Document No.: PREV199698809496. Phase I clinical trials with the **immunoconjugate BR96**-doxorubicin. Slichenmyer, W. J.; Bookman, M. A. (1); Gilewski, T. A.; Murray, J. L.; Saleh, M. N.; Dougan, M. (1); Healey, D. (1); Onetto, N. (1). (1) Fox Chase Cancer Center, Philadelphia, PA USA. Abstracts of Papers American Chemical Society, (1996) Vol. 211, No. 1-2, pp. CARB 32. Meeting Info.: 211th American Chemical Society National Meeting New Orleans, Louisiana, USA March 24-28,

1996 ISSN: 0065-7727. Language: English.

L11 ANSWER 11 OF 13 CAPLUS COPYRIGHT 2001 ACS

1995:731714 Document No. 123:104987 Ribosome-inactivating protein isolated from the plant Bryonia dioica. Siegall, Clay B.; Gawlak, Susan L.; Marquardt, Hans (Bristol-Myers Squibb Co., USA). PCT Int. Appl. WO 9511977 A2 19950504, 81 pp. DESIGNATED STATES: W: AU, CA, JP; RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1994-US12382 19941025. PRIORITY: US 1993-141891 19931025; US 1994-324301 19941020.

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AB A new ribosome-inactivating protein, bryodin 2, was isolated from the plant *Bryonia dioica*. This ribosome-inactivating protein (RIP) is a type I RIP having a single polypeptide chain and no cellular receptor domain. Like many type I RIPs, bryodin 2 has a mol. wt. of approx. 27,000 daltons and pI of 9.5. Bryodin 2 differs from previously identified ribosome-inactivating proteins in its amino acid compn., amino acid sequence, and toxicity in vitro and in vivo. Amino acid sequences of peptide fragments of bryodin 2 were used for the design of degenerate oligonucleotides for the cloning and isolation of cDNA for bryodin 2.

The cDNA encodes an amino acid sequence of 282 amino acids, including a 21-amino-acid signal peptide. Bryodin 2 is useful, as are other type I ribosome-inactivating proteins, as an abortifacient, immunomodulator, antitumor, or antiviral agent. Comps. comprising bryodin 2 as an **immunoconjugate** or fusion mol. are particularly useful to kill cells of a target population. Thus, bryodin 2 is conjugated via a hindered disulfide linkage to the chimeric monoclonal antibody **Br96** specific for the **Lewis Y** determinant and capable of internalizing within the tumor cells to which it binds. Cell killing activity of chiBr96-bryodin 2 immunotoxin conjugates for H3396 tumor cells displayed an EC50 of 100 pM.

L11 ANSWER 12 OF 13 BIOSIS COPYRIGHT 2001 BIOSIS
1995:456888 Document No.: PREV199598471188. Affinity maturation of the **BR96** anti-carcinoma antibody by codon-based mutagenesis. Yelton, Dale E. (1); Rosok, Mae Joanne; Cruz, Gina; Cosand, Wesley L.; Bajorath, Juergen; Hellstrom, Ingegerd; Hellstrom, Karl Erik; Huse, William D.; Glaser, Scott M.. (1) Bristol-Myers Squibb Co., 3005 First Ave., Seattle, WA 98121 USA. Journal of Immunology, (1995) Vol. 155, No. 4, pp. 1994-2004. ISSN: 0022-1767. Language: English.

AB We have increased up to 65-fold the avidity of **BR96**, a mAb recognizing **Lewis Y** (Le-y)-related Ags expressed on the surface of many human carcinomas. Libraries of mutations in the complementarity-determining regions (CDRs) of **BR96** were constructed in an M13 phage Fab expression vector by codon-based mutagenesis, a method that efficiently introduces large numbers and potentially all combinations of amino acid substitutions. Two mutants that improved the affinity of **BR96** to tumor Ag were identified by screening the libraries on carcinoma cell lines. One mutant, M1, at position 97 (Asp to Ala) in CDR3 of the heavy chain, resulted in an 8- to 10-fold improvement in Ag binding, as assessed by ELISA. A second mutant, M2, at position 53 (Gly to Asp) in CDR2 of V-H increased binding three- to fivefold. When these mutations were combined, the resulting Fab M3 was improved approximately 30-fold. An additional library was constructed in CDR1 of M1. M4, a mutation with three amino acid substitutions in CDR1, was isolated by screening the library with an enzyme conjugate of synthetic Le-y tetrasaccharide (sLe-y). This mutant improved **BR96** Fab affinity to sLe-y an estimated 15- to 20-fold by ELISA, and 14-fold as measured by surface plasmon resonance. The M4 IgG had 65-fold improved avidity to sLe-y relative to the **BR96** IgG. The mutants will be useful for comparison of the efficacy of Abs with different affinities for delivery of cytotoxic agents to tumor cells.

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L11 ANSWER 13 OF 13 MEDLINE

DUPLICATE 6

93318145 Document Number: 93318145. Cure of xenografted human carcinomas by **BR96-doxorubicin immunoconjugates** [published erratum appears in Science 1994 Feb 25;263(5150):1076]. Trail P A; Willner D; Lasch S J; Henderson A J; Hofstead S; Casazza A M; Firestone R A; Hellstrom I; Hellstrom K E. (Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ 08543.) SCIENCE, (1993 Jul 9) 261 (5118) 212-5. Journal code: UJ7. ISSN: 0036-8075. Pub. country: United States.

Language:

English.

AB **Immunoconjugates (BR96-DOX)** were prepared between chimeric monoclonal antibody BR96 and the anticancer drug doxorubicin. The monoclonal antibody binds an antigen related to **Lewis Y** that is abundantly expressed at the surface of cells from many human carcinomas; it has a high degree of tumor selectivity and is internalized after binding. **BR96-DOX** induced complete regressions and cures of xenografted human lung, breast, and colon carcinomas growing subcutaneously in athymic mice and cured 70 percent of mice bearing extensive metastases of a human lung carcinoma. Also, **BR96-DOX** cured 94 percent of athymic rats with subcutaneous human lung carcinoma, even though the rats, like humans and in contrast to mice, expressed the **BR96** target antigen in normal tissues.

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